REMARKS

I. Claim Amendment

Claims 1, 12, and 20 have been amended to correct a typographical error and to more particularly point out the claimed invention. Claim 20 has also been amended to recite that cancer is selected from the group consisting of breast, colon, lung, prostate cancers and leukemia. Support for this amendment is found in Examples 5 and 6 of the Exemplification section of the instant disclosure as well as in Claims 28 and 29, now cancelled. This amendment introduces no new matter.

New Claims 30-39 have been added.

Claim 30 is drawn to the subject matter of Claim 1, wherein the carboxylate anion is selected from aliphatic C2-C6 di- and C3-C8 tri-carboxylic acids. Support for this amendment is found on page 10, lines 4-19 of the specification as filed and, specifically, Table 3, pages 27-28. Claim 31 is drawn to the subject matter of Claim 12, wherein the carboxylate anion is selected from C2-C6 aliphatic di- and tri-carboxylic acids. Claim 32 is drawn to the subject matter of Claim 9 (see also Table 3, pages 27-28 of the specification as filed) and is cast as dependent on Claim 31. Claim 33 is drawn to amonafide malate, as recited in Claim 10, 19 and 27. Claim 34 is drawn to the subject matter of Claim 20, wherein the carboxylate anion is selected from aliphatic C2-C6 di- and C3-C8 tri-carboxylic acids. Claim 35 is drawn to the subject matter of Claim 9 (see also Table 3, pages 27-28 of the specification as filed) and is cast as dependent on Claim 34. Claim 36 is drawn to amonafide malate, as recited in Claim 10, 19 and 27. Claims 37-39 recite a aliphatic C2-C6 di- and C3-C8 tri-carboxylic acid salt of amonafide. This amendment introduces no new matter.

II. Rejection of Claim 1-29 under 35 U.S.C. §112, 2nd Paragraph

Claims 1-29 are rejected under 35 U.S.C. §112, 2nd Paragraph, as being indefinite. The Examiner stated that the recitation of R2 as $-N^{+}HR6R7$ in the definition of R1 within Claim 1 has no antecedent basis as the definition of R2 recites only $-N^{+}HR6R7X^{-}$.

Claims 1, 12 and 20 have now been amended to correct this typographical error. Applicants believe that this amendment obviates the Examiner's objection.

III. Rejection of Claims 1-29 under 35 U.S.C. §103(a)

Claims 1-29 are rejected under 35 U.S.C. §103(a) over Brana I (U.S. Pat No. 4,204,063) in view of Brana II (U.S. Pat. No. 5,420,137), Berge (J. of Pharm. Sci. (1977) 66(1):1-19) and Zee-Cheng (U.S. Pat. No. 4,614,820).

The Examiner stated that Brana I discloses N-aminoalkyl-naphthalimide compounds, including amonafide, and their hydrochloric and methanesulfonic salts as anti-tumor agents. The Examiner stated that Zee-Cheng discloses salts of tartaric, malonic, citric, succinic, fumaric and maleic acids as pharmaceutically acceptable salts. The Examiner further stated that Berge teaches that organic acid salts of basic drugs, such as amines, are more soluble in water than the corresponding inorganic salts, including halides. The Examiner concluded that the invention of Claims 1-29 is obvious because one skilled in the art would have been motivated by Berge to replace hydrochloric or methanesulfonic acid of Brana I by an organic acid of Zee-Cheng.

The Examiner also stated that the comparative data presented in Table 4, pages 31-32 of the instant application, fails to render Claims 1-29 non-obvious over the prior art because higher solubility of organic acid salts of amonafide is not unexpected in view of the above cited references.

Applicants respectively disagree with the Examiner's conclusion and submit that the case of obviousness is rebutted by the available evidence of unexpected results.

1. Summary of the Applicants' Invention

The claimed invention is directed to an organic carboxylic salts of compounds of formula (I), pharmaceutical compositions comprising the same and methods of treating breast cancer, colon cancer, lung cancer, prostate cancer and leukemia comprising the step of administering to the subject an effective amount of a compound of formula (I).

The claimed organic carboxylic salts possess an unexpected advantage over hydrochloric and methanesulfonic salts of Brana. Referring to Table 3, pages 27-28, of the specification as filed, the purity of recrystallized organic acid salts of amonafide was in every tested case but one significantly greater than the corresponding recrystallized hydrochloric and methanesulfonic salts, thus resulting in unexpected ease of purification.

Furthermore, Examples 5 and 6 demonstrate that a representative organic salt of the invention, the malate, was effective both *in vitro* and *in vivo* for treating not only leukemia, but also breast, colon, lung and prostate cancers.

2. Ease of Purification of the Salts of the Present Invention is Unexpected and Non-obvious in View of Brana, Zee-Cheng and Berge

The evidence provided in the Table 3, pages 27-28, of the specification as filed, shows that the salts of the present invention unexpectedly are more readily purified than the hydrochloride and methanesulfonate salts of Brana. The purity of organic carboxylic salts of the invention is significantly higher after one re-crystallization. After one re-crystallization, all tested organic carboxylic acid salts of amonafide except one had purity above 98% (amonafide malonate had a purity of 97%), whereas amonafide hydrochloride and methanesulfonate had re-crystallized purities of 94% and 93% respectively. Eight out of fifteen tested organic carboxylic acid salts had purity of 99% or above.

The unexpected superiority of the organic salts of the present invention does not depend on the method by which the salts are prepared. Table 3 compares the salts prepared by the novel method of Example 1 (the subject matter of the U.S. Patent No. 6,693,198) to the salts prepared by the methods of prior art (Brana, Zee-Cheng and Example 2). Thus, the purity of recrystallized amonafide hydrochloride prepared by the novel method of Example 1 was lower than the purity of any other recrystallized organic salt of amonafide prepared by the same method, except malonate. The purity of recystallized amonafide hydrochloride prepared by methods of prior art (Brana, Zee-Cheng or Example 2) was lower than that of every tested organic acid salt of amonafide prepared by the same method. It follows, therefore, that superiority of the organic acid salts of the present invention lies not in their method of preparation, but in their unexpected ease of purification.

The Examiner argues that it would be obvious for one skilled in the art to replace the hydrochloric salts of Brana by the organic salts of Zee-Cheng in view of Berge's teaching that the organic salts or basic drugs are more soluble in water. Applicants note that water solubility and ease of purification (purity after one recrystallization) are not one and the same. Specifically, the Examiner's attention is directed to the entries for amonafide methanesulfonate

and for amonafide adipate, citrate and fumarate. Each of these compounds was recrystallized from 25 ml of aqueous solvent (water/ethanol) per gram of salt. Yet, the purity of recrystallized organic salts (98% for adipate, 99.1% for citrate and 98.9% for fumarate) is significantly higher than that for methanesulfonate (93%). Even more telling is the data for aspartate (30 ml/g, 98.7%), oxoglutarate (30 ml/g, 98.1%) and salicylate (35 ml/g, 98.7%). These salts were less soluble than methanesulfonate, yet produced higher purity end products.

It follows therefore, that the unexpected advantage of the salts of the instant invention, *i.e.* the ease of their purification, is independent from their method of synthesis or their solubility in water or any other solvent. Purity is a property of paramount importance in pharmacopoeia: a compound which is 94% pure is unlikely to be pharmaceutically acceptable without further purification and the attendant decrease in yield and increase in cost.

Accordingly, one skilled in the art would ***not*** be motivated to replace the hydrochloride of Brana by the organic acids of Zee-Cheng by Berge's teaching of higher water solubility since the water solubility alone does not directly address the issue of higher purity of organic salts. Nor does Zee-Cheng's disclosure that salts of tartaric, malonic, citric, succinic fumaric or maleic acid are pharmaceutically acceptable, without more, obviate the present invention. Indeed, the present invention does not claim the organic acids, but the salts of compounds of formula (I). Zee-Cheng, however, discloses a compound that is structurally distinct from that of formula (I) and, therefore, is not properly combinable with Brana. (*In re Grabiak* 226 USPQ 870 (CAFC 1985).)

In summary, Applicants submit that Claims 1-26 as well as new Claims 30-39 are not only novel but also non-obvious in view of Brana, Zee-Cheng and Berge. None of the cited references teaches or suggests that replacing hydrochloric or methansulfonic anion with that of an organic acid would result in a purer and cheaper active compound. None of the cited references contains any suggestion that such replacement would be successful. Yet, Applicants discovered the unexpected ease of purification of organic carboxylic salts of compounds of formula (I). Applicants submit that the obviousness rejection has been overcome.

3. The Unexpected Advantages of Applicants' Invention Extends Over the Full Scope of Claims 1-26 and new Claims 30-39

In view of a large number of examples and structural dissimilarities between the tested compounds, Applicants respectfully submit that the evidence presented in Table 3 shows that the unexpected advantages of the claimed organic acid salts extend through the full scope of Claims 1-26 and 30-39, which are therefore novel and non-obvious.

As presented in Table 3, of the fifteen organic carboxylic salts of amonafide tested, all fifteen possess properties that allow them to be more easily purified than the salts of the prior art. The fifteen carboxylate anions span a broad spectrum of structures: from a two-carbon monocarboxylic glycolate to a six-carbon tri-carboxylic citrate, and include saturated and unsaturated, hydroxy, keto and amino acids.

Applicants further submit that new Claims 30-39 are novel and non-obvious. Claims 30, 31, 34 and 37-39 are drawn to a subgenus of the genus claimed in Claim 1. Species representing this subgenus are listed in Table 3 and are the subject matter of Claims 32 and 35 as well as the original Claim 9. These species include:

C2-C8 aliphatic dicarboxylic acids: malonate, adipate, succinate, fumarate, and maleate.

Hydroxy C2-C6 dicarboxylic acids: malate, and tartrate.

A keto C5 dicarboxylic acid: 2-oxo-glutarate.

A C6 tricarboxylic acid: citrate.

Thus, one or more species of the subgenus of organic carboxylic acids of Claim 1, claimed in new Claims 30-39, has been shown to possess unexpectedly superior ease of purification. This evidence demonstrates that not only the subgenus claimed in Claims 30-39 (as well as in the original Claim 9) possesses the unexpected advantageous property, but also that the full scope of the genus of Claims 1-26 can reasonably be expected to possess the unexpected ease of purification.

It is additionally noted that Claims 37-39 are directed to aliphatic C2-C6 di- or C3-C8 tri-organic salts of one compound, amonafide.

Additionally, Applicants submit that just as amonafide malate and glycolate were deemed novel and non-obvious (claims drawn to amonafide malate and glycolate were allowed and issued in the U.S. Patent No. 6,693,198), so should Claims 10, 19, 27 as well as new Claims 33 and 36, drawn to the amonafide malate, a pharmaceutical compositions comprising same and a

method of treating breast cancer, colon cancer, lung cancer, prostate cancer and leukemia comprising the step of administering to the subject an effective amount of amonafide malate.

Reconsideration and withdrawal of the rejection are respectfully requested.

IV. Rejection of Claims 20-29 under 35 U.S.C. §112, First Paragraph

Claims 20-29 are rejected under 35 U.S.C. §112, 1st paragraph, as not enabled.

The Examiner acknowledged that the specification enables the use of amonafide salt compounds to treat leukemia, breast, colon, lung or prostate cancer. The Examiner, however, stated that the specification does not reasonable provide enablement for *all* types of cancer.

The Examiner further stated that the assertion that all the structurally diverse compounds, including those with R3 and R4 and/or R6 and R7 forming heterocyclic rings of any size, are effective for treating cancer does not commensurate with the scope of objective enablement in view of the high degree of unpredictability in anti-tumor art. It is Applicants' understanding that the Examiner is rejecting Claim 20 as not enabled for *all* recited structures.

1. Rejection of Claims 20-29 as Non-Enabled for *all* Types of Cancer

Applicants have amended Claim 20 to recite the types of cancer that the Examiner acknowledged to be enabled (Office Action of June 9, 2004, page 4, section 4). New Claim 34 also recites beast, colon, lung and prostate cancers as well as leukemia.

Applicants believe that this amendment obviates the Examiner's objection. Reconsideration and withdrawal of rejection is respectfully requested.

2. Rejection of Claims 20-29 as Non-Enabled for *all* Recited Structures

Applicants disagree with the Examiner's conclusion that Claim 20, and therefore new Claim 34, do not commensurate with the scope of objective enablement.

U.S. Pat. No. 4,204,063 to Brana *et al.* (Brana I) teaches that thirty three compounds, hydrochloric salts of N,3-disubstituted naphthalimide, have cytotoxic activity. See Brana I, columns 8-9 and U.S. Pat. No. 5,183,821 to Brana *et al.* (Brana II), column 2, lines 21-25. These compounds include a broad spectrum of structurally varied substituents, including heterocycles of 5 to 6 atoms with one or two heteroatoms.

Brana II discloses that 14 of these compounds have variable activity against leukemia (Brana II, columns 25-26). Brana II also discloses that, as remarked by the Examiner, hydrochloric salt of at least one of these compounds, namely amonafide, has activity not only against leukemia, but also reproducible activity against unrelated cancers such as melanoma and colon cancer (Brana II, column 6, lines 20-35).

The instant disclosure demonstrates that organic salts of amonafide are active not only against leukemia, but also against colon, breast, lung and prostate cancers.

In view of the teachings that thirty three N,3-disubstituted naphthalimides have cytotoxic properties with fourteen compounds having activity against leukemia and at least one having activity against other cancers, it stands to reason that the compounds of formula (I) of the instant disclosure can be expected to have biological activity similar to other members of the family.

Applicants submit that the instant specification reasonably enables one skilled in the art to make and use the inventive salts of Claim 20 for treating the types of cancer recited in Claim 20 as amended and new Claim 34. Reconsideration and withdrawal of rejection is respectfully requested.

V. Double Patenting Rejection of Claims 11-29

Claims 11-29 are rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1 and 2 of U.S. Pat. No. 6,693,198 in view of U.S. Pat. No. 4,204,063 (Brana I).

The Applicants enclose herewith a Terminal Disclaimer under 37 C.F.R. § 1.321(c) in which the owner of a 100 percent interest in the instant application, Xanthus Life Sciences, Inc., disclaims the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154 to 156 and 173, as presently shortened by any terminal disclaimer, of U.S. Pat. No. 6,693,198.

The rejection is moot with the submission of the Terminal Disclaimer. Withdrawal of the rejection is respectfully requested.

V. New Claims 30-39 are Novel and Non-obvious

Applicants introduced new Claims 30-39 directed to the C2-C6 di- and C3-C8 tri-carboxylic acids of compounds of formula (I), including amonafide, as well as to pharmaceutical compositions comprising said compounds and methods of treating cancer by administering an effective amount of said compounds.

Applicant submit that new Claims 30-39 are both novel and non-obvious in view of Brana, Zee-Cheng and Berge.

While Applicants discovered the unexpected ease of purification of organic carboxylic salts of compounds of formula (I), none of the cited references teaches or suggests that replacing hydrochloric or methansulfonic anion with that of an organic acid would result in a purer and cheaper active compound and none of the cited references contains any suggestion that such replacement would be successful.

Applicants further submit that, in view of a large number of examples and structural dissimilarities between the organic acid salts presented in Table 3, the unexpected advantages of the claimed organic acid salts extend through the full scope of Claims 30-39. Thus, one or more species of the subgenus of organic carboxylic acids claimed in new Claims 30-39, has been shown to possess unexpectedly superior ease of purification.

Furthermore, Applicants submit that new Claims 34 and 39 are enabled for the full scope of the recited strictures, because, in view of the teachings that thirty three N,3-disubstituted naphthalimides have cytotoxic properties with fourteen compounds having activity against leukemia and at least one having activity against other cancers, one skilled in the art could reasonably expect that the compounds of formula (I) of the instant disclosure will have biological activity similar to other members of the family. Accordingly, the instant specification reasonably enables one skilled in the art to make and use the inventive salts of new Claims 34 and 39.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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